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EXAMINER	
LEITH, PATRICIA A	
ART UNIT	PAPER NUMBER
1655	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO.e-Office.rdg@boehringer-ingelheim.com

Office Action Summary	Application No.	Applicant(s)	
	10/743,170	ESPERESTER ET AL.	
	Examiner	Art Unit	
	Patricia Leith	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 5-16, 30 and 34-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-16, 30 and 34-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1, 5-16, 30 and 34-36 are pending in this application for US patent, claim 36 being newly added in the most recent amendment submitted on 9/21/2010.

Claims 1, 5-16, 30 and 34-36 were examined on their merits.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5-16 and 29-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,991,816 (reference provided in the IDS submitted by Applicants on 12/17/07) in view of Struengmann (US 6,284,269) in view of Mathowitz, E. (1999) in view of Esperester et al. (WO 01/28363 A1) in view of Abramovici et al. (US 6303626) in view of Saslawski et al. (US 6,426, 087).

Claims 1-8 of '816 teach a composition 'consisting essentially of' an aqueous red vine leaf extract and a pharmaceutical carrier.' Here, 'a pharmaceutical carrier' is not limited to one carrier as reading the phrase plainly, 'a pharmaceutical carrier' may mean numerous individual carriers which are combined to create 'a pharmaceutical carrier.' The claims (1-8) of '816 did not teach the specific carriers of the claimed invention, nor the specific amounts as claimed.

Struengmann (US 6,284,269) disclosed conventional tablet additives such as hydrogen phosphate, colloidal anhydrous silica, sodium starch, magnesium stearate, microcrystalline cellulose (see example V/7, col's 10-11) as well as plasticizers such as polyethylene glycol (see claim 10). Thus, it was known that all of the tablet ingredients as Instantly claimed were conventional tablet ingredients, known at the time the invention was made.

Mathowitz, E. (1999) disclosed the conventional practice of addition of controlled-release coatings (films) in tablet manufacture (see pages 302 and 306-309).

Abramovici et al. (US 6303626) disclosed a tablet comprising 2% anhydrous colloidal silica, 2.1% active ingredient and the remainder consisting of conventional excipients (see, e.g., Example 9, col. 12). See also, Example 11, where they disclose a tablet comprising 2% anhydrous colloidal silica and 12.5% active ingredients, with the remainder of the tablet being conventional excipients (see Col. 13).

Esperester et al. (WO 01/28363 A1) taught oral compositions such as capsules and tablets comprising an aqueous extract of red vine leaf for treatment of venous insufficiency:

> In a preferred embodiment, the dietary supplement is in a form suitable for oral administration, in particular in a solid dosage form, i.e. **a capsule or tablet, that consists of 20 to 60% of aqueous red vine leaf extract with a high flavonoid content of 2-15**%. Another preferred dosage form is that of drops containing 3 to 90% of extract. Further suitable administration forms may be coated tablets, syrups, or the like (see p. 3).... ..... **For the preparation of solid dosage forms the thick extract is dried, for instance by use of a vacuum drying oven or a vacuum drying conveyer. Carriers or excipients may be added during drying to facilitate further processing of the extract. Such carriers or excipients may be silicon dioxide, maltodextrine, glucose syrup, cellulose and others** (see paragraph bridging pp. 4-5, emphasis added).

It is noted that silicon dioxide is colloidal silica. Also, it is clear that because the carriers are added during drying, that the silica and other carriers are in dried form, and more than likely in powdered form even though the reference does not explicitly teach that the carriers are in powdered form.

It is apparent that Esperester et al. clearly taught drying of the extract prior to admixing into a tablet with a carrier such as silicon dioxide (colloidal silica).

Also, please see claims 1-15 and especially claim 9 which states:

9. A method according to claim 8 wherein said red vine leaf extract is present within the range of 1 to 50% related to the total mass of the dietary supplement composition.

Saslawski et al (US 6,426, 087) teaching preferred methods for compounding their medicinal tablets :

(67) As a guide, the quantity of gastro-resistant film-coating excipients varies between 0.5 and 9% by weight of the tablet.

(68) **These tablets may be bare, but are preferably film-coated. The film-coating envisaged will make it possible to avoid an unpleasant taste by bringing about masking of the taste**. It may participate in modifying the release of the active ingredient and/or of the promoting agent. **A gastro-resistant film-coating will make it possible to avoid any release in the stomach; a film-coating which is more hydrophobic and insensitive to pH** variations will contribute more towards extending the kinetics of dissolution. Depending on the role attributed to the film-coating, persons skilled in the art will be able to choose the film-forming agent from among the following categories: cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), ethyl cellulose, cellulose acetophthalate, cellulose acetopropionate, cellulose trimelliate, the polymers and copolymers of methacrylic acid and its derivatives. The film-forming agent may be supplemented with: plasticizers

> (such as polyoxyethylene glycols of high molecular weight, esters of polyacids such as citric acid or phthalic acid) fillers (such as talc, metal oxides such as titanium oxide) colorants chosen from those usable and approved by the pharmaceutical and food industries.

Hence, one of ordinary skill in the art would have been motivated to use a film coating between 0.5 and 9%, a range which overlaps with applicants' claimed range of 'greater than 1.4 to 10%' in order to hinder unpleasant taste and to ensure that the pharmaceutically active aqueous red vine extract was not degraded in the stomach thus ensuring better bioavailability of the active ingredient. It would have been obvious to create a tablet comprising aqueous red vine leaf extract with an enteric coating in order to shield the active ingredients of the extract from the acidic environment of the stomach in order to allow the active ingredients to pass undestructed into the small intestine for absorption into the bloodstream. It is clear from the teachings of Bilgrami et al. that the active ingredients enter into the bloodstream. Therefore, one of ordinary skill in the art would have easily recognized that protection of the extract would have been advantageous in order to prevent the degradation of the active components in order to optimize the effectiveness of the medicinal extract. Use of tablet films to protect tablet disintegration in the stomach were well-known and known to be used in the amounts as Instantly claimed and thus, the concept as claimed is not deemed inventive in view of the combined teachings of the prior art.

It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal concentrations of components because concentration of aqueous red vine leaf extract is an art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art. Although the prior art do not teach the particular combination of carriers which are added to the red vine extract or all the various permutations of concentration ranges as claimed, it would be conventional and within the skill of the art to identify the optional concentrations of a given excipient because (1) the selection of appropriate concentration of excipients to stabilize red vine extract for the intended purpose of preventing its denaturation and decomposition during storage are conventional and within the skill in the art, and (2) hydrogen phosphate, colloidal anhydrous silica, sodium starch, magnesium stearate, microcrystalline cellulose and polyethylene glycol are well known in the art as excipients to used for tableting active ingredients. The incorporation of known active ingredients into tablets with conventional carriers was well within the purview of the ordinary artisan at the time the invention was made, and is hence considered *prima facie* obvious.

Applicants argue that this rejection is obviated due to their contention that the arguments against the rejection placed under 35 USC 103(a) are sufficient to overcome the rejection under 35 USC 103(a) which also pertain to this Double Patenting rejection. However, said arguments are not found convincing with regard to the rejection placed under 35 USC 103(a) and are thus concurrently not found convincing to overcome this Double Patenting rejection. Please see the Examiner's answer to Applicants' arguments which follow the rejection under 35 USC 103(a).

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5-16, 30 and 34-35 remain rejected and claim 36 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Esperester et al. (WO 01/28363 A1) in view of Bilgrami et al. (1993) in view of Struengmann (US 6,284,269) in view of Mathowitz, E. (1999) in view of Saslawski et al. (US 6,426, 087) in view of Abramovici et al. (US 6303626) and in view of Lieberman, H., Ed. et al. (1990).

Esperester et al. (WO 01/28363 A1) taught oral compositions such as capsules and tablets comprising an aqueous extract of red vine leaf for treatment of venous insufficiency:

> In a preferred embodiment, the dietary supplement is in a form suitable for oral administration, in particular in a solid dosage form, i.e. **a capsule or tablet, that consists of 20 to 60% of aqueous red vine leaf extract with a high flavonoid content of 2-15**%. Another preferred dosage form is that of drops containing 3 to 90% of extract. Further suitable administration forms may be coated tablets, syrups, or the like (see p. 3).... ..... **For the preparation of solid dosage forms the thick extract is dried, for instance by use of a vacuum drying oven or a vacuum drying conveyer. Carriers or excipients may be added during drying to facilitate further processing of the extract. Such carriers or excipients may be silicon dioxide, maltodextrine, glucose syrup, cellulose and others** (see paragraph bridging pp. 4-5, emphasis added).

It is noted that silicon dioxide is colloidal silica and is anhydrous (silicon dioxide does not contain water). Also, it is clear that because the carriers are added during

drying, that the silica and other carriers are in dried form, and more than likely in powdered form even though the reference does not explicitly teach that the carriers are in powdered form.

It is apparent that Esperester et al. clearly taught drying of the extract prior to admixing into a tablet with a carrier such as silicon dioxide (colloidal anhydrous silica).

Also, please see claims 1-15 and especially claim 9 which states:

> 9. A method according to claim 8 wherein said red vine leaf extract is present within the range of 1 to 50% related to the total mass of the dietary supplement composition.

Pertaining to claims 34 and 35 which state that the red vine leaves are collected when the flavonoids have reached an optimum, drying and crushing the leaves, cutting the leaves to pieces, extracting the leaves with water from 60˚C to 80˚ C for 6 to 10 hours, concentrating and drying the extract and adding up to 10% by weight of colloidal anhydrous silica:

Esperester et al. specifically taught that their aqueous red vine leaf extract was made by collecting leaves when the flavonoids had reached an optimum, whereby the leaves are dried and crushed, cut to pieces and extracted at a temperature from 60˚C to 80˚ C for 6 to 10 hours (e.g., via percolation) and concentrated via evaporation and dried (e.g., by use of a vacuum dryer) (see p. 4, line 18- p. 5, line 2).

Esperester et al. did not specifically disclose an embodiment which included colloidal silica and an aqueous extract of red vine leaf in the claimed amounts, a binder such as microcrystalline cellulose, a filler such as hydrogen phosphate or magnesium stearate, a plasticizer, a colorant or the particular amounts of each constituent in the tablet.

Bilgrami et al. (1993) studied the preventative effects of aqueous *Vitis vinefera* L. leaf. (red vine leaf) on nephrotoxicosis due to ingestion of the micotoxin citrinin. Bilgrami et al. discovered that *V. vinefera* L. leaf water extract administered by intubation to albino Swiss mice challenged with citrinin possessed greater toxicity prevention than cortisone (see entire reference, especially Table 1 and p. 482, col. 2). Hence, prior to Applicants' Invention, aqueous red vine leaf extract was a composition with known pharmaceutical value.

Struengmann (US 6,284,269) disclosed conventional tablet additives such as hydrogen phosphate, colloidal anhydrous silica, sodium starch, magnesium stearate, microcrystalline cellulose (see example V/7, col's 10-11) as well as plasticizers such as polyethylene glycol (see claim 10). Thus, it was known that all of the tablet ingredients

as Instantly claimed were conventional tablet ingredients, known at the time the invention was made.

Mathowitz, E. (1999) disclosed the conventional practice of addition of controlled-release coatings (films) in tablet manufacture (see pages 302 and 306-309). "Coatings often contain several components in addition to the primary component polymeric species, which provides the backbone of the coating. Some of the secondary coating components may be deliberately added in order to modify the permeability of the primary polymer by providing channels or pores within the coating…Other materials, such as plasticizers, although they are added for entirely different reasons, can, in some instances, significantly modify drug release rates.." (p. 302, Col. 1). "The outer coating protects the drug until the small intestine is reached. The inner coating…is of such a thickness and composition that the drug is released in the colon. Multilamellate coatings in which each coating has a different function to perform offer the potential of developing very sophisticated, controlled release coating system." (*Id*). See Table 1 for conventional materials such as coatings and plasticizers used in tablet films (p. 307). Additionally, Mathowitz further taught "Coatings may well contain other components, such as colors or antioxidants, but specific attention is not given to components the primary function of which is not covered by one of these three categories."

Mathowitz discloses all of the claimed tablet film components; e.g., claim 15 comprises 1) a film former: Applicants' specification indicates that a preferred film

former is hypromellose. Hypromellose is short for 'hydroxypropyl methylcellulose which is disclosed by Mathowitz as a coating (see Table 1), 2) a plasticizer: Table 1 of Mathowitz discloses 9 types of conventional plasticizers, 3) a 'coating' agent: See enteric coatings in Table 1 of Mathiowitz (these are all coating agents) and 4) a coloring agent which is taught by Mathowitz at p. 307, col. 1 (as recited above).

Saslawski et al. (US 6,426, 087) taught a galenic formulation of guanylguanidine (see Abstract and Claims). This Patent by Saslawski et al. teaches various conventional means for tableting a pharmaceutical preparation; for example, Saslawski et al. explain that:

> It may also be noted that the pharmaceutical dosage forms of the invention ensure excellent reproducibility of the results, while allowing increased control of the rate of release during the phase of prolonged release of the active ingredient. By using the pharmaceutical dosage forms of the invention, it becomes **possible to optimize the availability of the active ingredients in the body taking into account both the tolerance of the subject to the active ingredient and the pharmacokinetic and metabolic profiles of the active ingredient.**
>
> (10) The tablets of the invention are moreover advantageous from the point of view of the formulation of the active ingredients since a judicious choice of the excipients leads to tablets with high concentrations of active ingredients.
>
> The tablets according to the invention may comprise, in combination with the absorption-promoting agent, one or more additional excipients so as to obtain mono- or polyphase tablets**. Persons skilled in the art will choose these excipients according to the desired final properties, the application envisaged or so as to overcome a disadvantage linked to the method of manufacturing the tablets.**
>
> (56) These excipients exist especially among the following categories: diluents, binders, lubricants, antioxidants, colorants, sweeteners, flavourings and acidulants, wetting agents, hydrophilizing agents such as sorbitol and cyclodextrins, osmotic agents such as mannitol, pH regulators, stabilizing

agents such as trehalose and mannitol, adsorbants, chelating and sequestering agents and gastro-resistant film-coating excipients of the type including cellulose acetyl phthalate and polymethacrylates.

By way of example, any one of the following diluents or a combination thereof may be chosen: calcium carbonate, calcium sulphate, sucrose, dextrates, dextrin, dextrose, dicalcium phosphate dihydrate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, cellulose, microcrystalline cellulose, sorbitol, starches, pregelatinized starch, talc, tricalcium phosphate and lactose.

(58) Among the binders, there may be mentioned: gum arabic, gum tragacanth, guar gum, alginic acid, sodium alginate, sodium carboxymethylcellulose, dextrin, gelatin, hydroxyethylcellulose, hydroxypropylcellulose, liquid glucose, magnesium and aluminium silicate, maltodextrin, povidone, pregelatinized starch, starch and zein.

(59) The lubricants are glidants (such as anhydrous silicate, magnesium trisilicate, magnesium silicate, cellulose, starch, talc or tricalcium phosphate) or alternatively antifriction agents (such as calcium stearate, hydrogenated vegetable oils, paraffin, magnesium stearate, polyethylene glycol, sodium benzoate, sodium lauryl sulphate, fumaric acid, stearic acid or zinc stearate and talc).

(63) Examples of adsorbants are bentonite, anhydrous colloidal silica, kaolin, magnesium and aluminium silicate, microcrystalline cellulose and cellulose.

(65) The quantities of these additives are those usually used in the art. In general, the binder may represent from 0.5 to 25% by weight, or better still from 2 to 5% by weight of the tablet.

(66) The lubricants are preferably incorporated into this tablet in an amount of 0.01 to 10% by weight.

(67) **As a guide, the quantity of gastro-resistant film-coating excipients varies between 0.5 and 9% by weight of the tablet.**

(68) **These tablets may be bare, but are preferably film-coated. The film-coating envisaged will make it possible to avoid an unpleasant taste by bringing about masking of the taste**. It may participate in modifying the release of the active ingredient and/or of the promoting agent. **A gastro-resistant film-coating will make it possible to avoid any release in the stomach; a film-coating which is more hydrophobic and insensitive to pH** variations will contribute more towards extending the kinetics of dissolution. Depending on the role attributed to the film-coating, persons skilled in the art will be able to choose the film-forming agent from among the following categories: cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), ethyl cellulose, cellulose acetophthalate, cellulose acetopropionate, cellulose

trimelliate, the polymers and copolymers of methacrylic acid and its derivatives. The film-forming agent may be supplemented with: plasticizers (such as polyoxyethylene glycols of high molecular weight, esters of polyacids such as citric acid or phthalic acid) fillers (such as talc, metal oxides such as titanium oxide) colorants chosen from those usable and approved by the pharmaceutical and food industries.

(69) The tablets of the invention are conventionally prepared by a method including the steps of granulation followed by compression. More precisely, the method of manufacture which is the subject of the invention comprises the steps consisting in: a) preparing a granule of an active substance from a pulverulent mixture of the active substance, to which there would have been added the absorption-promoting agent, preferably in liquid form, agents modifying the kinetics of dissolution, a binding agent and any other excipient which persons skilled in the art will judge to be necessary. The granule formed is called the inner phase. b) preparing, where appropriate, a pulverulent mixture, termed outer phase, comprising for example cohesion agents, glidants, lubricants. c) combining, by mixing, the inner and outer phases. It should be noted that all of the constituents of the outer phase may be added and mixed with the excipients of the inner phase during the preparation of the granule ready to be compressed. d) forming the tablet by compressing the mixture.

(70) Step (a) involves the granulation of powders of amorphous or crystallized particles. This granulation is carried out in a manner known per se and, for example, by a wet granulation method.

(71) The granulation method comprises five essential steps: (i) dry mixing of the various constituents, (ii) wetting, (iii) actual granulation, (iv) drying, and then (v) sizing.

(72) The dry mixing consists of mixing the pulverulent excipients entering into the composition of the granules.

(73) The wetting consists of adding to the pulverulent mixture the various constituents, a wetting liquid which may be water, or an aqueous or organic solution of binder or an alcohol. This is carried out in a mixer-kneader of the planetary, roller, projection or whirling type or a mixer-granulator of the rapid type.

(74) In step (a), the appropriate wetting liquid is water or an alcohol or an aqueous or organic solution of binder, as generally recommended in the art.

(75) According to a particularly preferred embodiment, the absorption-promoting agent is used as wetting liquid for the granulation.

(76) The drying may be carried out in an oven, or in a fluidized air bed dryer, or by microwave.

Abramovici et al. (US 6303626) disclosed a tablet comprising 2% anhydrous colloidal silica, 2.1% active ingredient and the remainder consisting of conventional excipients (see, e.g., Example 9, col. 12). See also, Example 11, where they disclose a tablet comprising 2% anhydrous colloidal silica and 12.5% active ingredients, with the remainder of the tablet being conventional excipients (see Col. 13).

Lieberman, H.A., Ed. et al. taught that granule strength and friability of tablets were dependent upon the base materials (i.e., carriers):

> A granule is an aggregation of component particles that is held together by the presence of bonds of finite strength. the strength of a wet granule is due mainly to the surface tension of liquid and capillary forces…Upon drying, the dried granule will have strong bonds resulting from fusion or recrystallization…Measurements of granule strength are, therefore, aimed at estimating the relative magnitude of attractive forces seeking to hold the granule together. The resultant strength of a granule is, of course, dependent upon the base material, the kind and amount of granulating agent used, the granulating equipment used and so on." (p. 308)

It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal concentrations of components because concentration of aqueous red vine leaf extract is an art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art. Although the prior art do not teach the particular combination of carriers which are added to the red vine extract or all the various permutations of concentration ranges as claimed, it would be conventional and within the skill of the art to identify the optional concentrations of a given excipient because (1) the selection of appropriate concentration of excipients to stabilize red vine extract for the intended purpose of preventing its denaturation and decomposition during storage are conventional and within the skill in the art, and (2) hydrogen phosphate, colloidal anhydrous silica, sodium starch, magnesium stearate, microcrystalline cellulose and polyethylene glycol are well known in the art as excipients to used for tableting active ingredients, colloidal anhydrous silica being a carrier specifically disclosed by Esperester et al. as being suitable for adding to aqueous red vine leaf extracts while drying to produce pharmaceutical dosage forms. The incorporation of known active ingredients into tablets with conventional carriers and adjusting the amounts of these carriers was well within the purview of the ordinary artisan at the time the invention was made, and is hence considered *prima facie* obvious.

Hence, it naturally follows that the use of 10% colloidal anhydrous silica (claim 34) is deemed an obvious variation of the teaching of Esperester et al. in view of the secondary references.

Although Esperester et al. did not disclose an explicit embodiment which showed a tablet comprising the claimed amounts of red vine leaf aqueous extract and colloidal silica, Esperester et al. clearly strongly suggested such a combination in that they plainly taught that a capsule or tablet comprising 20-60% of red vine leaf aqueous extract was advantageously added to a carriers such as silicon dioxide (colloidal silica) to make into tablets/capsules. Thus, it is clear that the tablet proposed by Esperester et al. would have contained from 40-80% carriers for the tablet. Although Esperester et al. did not specifically teach the amounts of the silica or cellulose as Instantly claimed, it is clear that because the capsule or tablet contained from 20 to 60% of the active ingredient (i.e., the aqueous extract of red vine leaves) that the carrier could have been present in an amount from 40-80% of the tablet. It is deemed that the adjustment of concentration of the carriers with respect to the active ingredients and other suitable carriers would have been well within the purview of the ordinary artisan at the time the invention was made because such adjustments were considered conventional in the art of pharmacology, especially considering that amounts of colloidal anhydrous silica for use in pharmaceutical compounding were known according to Abramovici et al. who incorporated 2% of this excipient into their tablet.

Although Esperester et al. did not disclose wherein the tablet was manufactured with 1-3% of a film, tablet filming was a conventional practice in the art for necessitating drug delivery to the small intestines. Clearly, as taught by Saslawski et al.:

> **(67) As a guide, the quantity of gastro-resistant film-coating excipients varies between <u>0.5 and 9%</u> by weight of the tablet.**
>
> (68) **These tablets may be bare, but are preferably film-coated. The film-coating envisaged will make it possible to avoid an unpleasant taste by bringing about masking of the taste**. It may participate in modifying the release of the active ingredient and/or of the promoting agent. **A gastro-resistant film-coating will make it possible to avoid any release in the stomach; a film-coating which is more hydrophobic and insensitive to pH** variations will contribute more towards extending the kinetics of dissolution. Depending on the role attributed to the film-coating, persons skilled in the art will be able to choose the film-forming agent from among the following categories: cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), ethyl cellulose, cellulose acetophthalate, cellulose acetopropionate, cellulose trimelliate, the polymers and copolymers of methacrylic acid and its derivatives. The film-forming agent may be supplemented with: plasticizers (such as polyoxyethylene glycols of high molecular weight, esters of polyacids such as citric acid or phthalic acid) fillers (such as talc, metal oxides such as titanium oxide) colorants chosen from those usable and approved by the pharmaceutical and food industries.

Hence, one of ordinary skill in the art would have been motivated to use a film coating between 0.5 and 9%, a range which overlaps with applicants' claimed range of 'greater than 1.4 to 10%' in order to hinder unpleasant taste and to ensure that the pharmaceutically active aqueous red vine extract was not degraded in the stomach thus ensuring better bioavailability of the active ingredient. It would have been obvious to create a tablet comprising aqueous red vine leaf extract with an enteric coating in order

to shield the active ingredients of the extract from the acidic environment of the stomach in order to allow the active ingredients to pass undestructed into the small intestine for absorption into the bloodstream. It is clear from the teachings of Bilgrami et al. that the active ingredients enter into the bloodstream. Therefore, one of ordinary skill in the art would have easily recognized that protection of the extract would have been advantageous in order to prevent the degradation of the active components in order to optimize the effectiveness of the medicinal extract. Use of tablet films to protect tablet disintegration in the stomach were well-known and known to be used in the amounts as Instantly claimed and thus, the concept as claimed is not deemed inventive in view of the combined teachings of the prior art.

It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal concentrations of aqueous red vine leaf extract because this extract is an art-recognized result-effective variable (i.e., having an advantageous effect on venous insufficiency) which would have been routinely determined and optimized in the pharmaceutical art. Although the claimed invention is not explicitly found in the prior art, the choice of carriers as Instantly claimed is deemed to be merely a matter of design choice. According to the prior art, especially established by Lieberman, H.A.,

Ed. et al. in addition to Saslawski et al., compounding of pharmaceuticals into tablets was routine and within the skill of the ordinary artisan at the time the invention was made. All of the carriers as Instantly claimed were recognized conventional carriers/additives for pharmaceutical tablets, most of the claimed compounds already being recognized for use in pharmaceutical tablets, some within the ranges set forth in Applicants' claims.

As taught by Saslawski et al.:

> It may also be noted that the pharmaceutical dosage forms of the invention ensure excellent reproducibility of the results, while allowing increased control of the rate of release during the phase of prolonged release of the active ingredient. By using the pharmaceutical dosage forms of the invention, it becomes **possible to optimize the availability of the active ingredients in the body taking into account both the tolerance of the subject to the active ingredient and the pharmacokinetic and metabolic profiles of the active ingredient.**
>
> (10) The tablets of the invention are moreover advantageous from the point of view of the formulation of the active ingredients since **a judicious choice of the excipients leads to tablets with high concentrations of active ingredients.**
>
> The tablets according to the invention may comprise, in combination with the absorption-promoting agent, one or more additional excipients so as to obtain mono- or polyphase tablets. **Persons skilled in the art will choose these excipients according to the desired final properties, the application envisaged or so as to overcome a disadvantage linked to the method of manufacturing the tablets.**

Further in view of Lieberman, H.A., Ed. et al. who taught that granule strength and friability of tablets were dependent upon the base materials (i.e., carriers), it is clear that the choice of type and percentage of particular carrier for use in pharmaceutical tablets are result effective, meaning that each carrier contributes to the

tablets overall strength and cohesiveness. This variability is clearly additionally associated with the components of tablet films as taught by Mathiowitz. Accordingly, it would have been conventional and within the skill of the art to identify the claimed concentrations of given tablet excipients and film components because (1) the selection of appropriate concentration of excipients and film components to stabilize red vine extract for the intended purpose of preventing its denaturation and decomposition during storage and to optimize drug delivery are conventional and within the skill in the art , and (2) hydrogen phosphate, colloidal anhydrous silica, sodium starch, magnesium stearate, microcrystalline cellulose and polyethylene glycol are well known in the art as excipients to used for tableting active ingredients. The incorporation of known active ingredients into tablets with conventional carriers was well within the purview of the ordinary artisan at the time the invention was made, and is hence considered *prima facie* obvious.

It is the opinion of the Examiner that the claimed invention is an obvious variation of the compositions disclosed by Esperester et al. and/or Bilgrami et al. respectively and is thus unpatentable. The carriers which are added to the known, medicinal product of an aqueous extract of red vine leaf were well-known in the art as conventional tableting excipients and thus, the addition of such known excipients and concentration adjustment thereof is deemed plainly obvious to one of ordinary skill in the art of pharmaceutical compounding. [If]… there are [a] finite number of identified, predictable solutions, [a] person of ordinary skill in art has good reason to pursue known

options within his or her technical grasp, and if this leads to anticipated success, it is likely product of ordinary skill and common sense, not innovation *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 U.S. 2007.

It is noted that claim 36, newly added in the most recent amendment submitted on 9/21/2010 limits the disintegrant of claim 9 to colloidal silica. Hence, claim 36 indicates that colloidal silica is present as an excipient, from 38 to 48 % by weight of the film coated tablet. As indicated above, silica was a known excipient in tablet manufacture. The addition of known, conventional tablet excipients and adjusting the concentration of the excipients to achieve a desired result is, in the opinion of the Examiner, obvious for the reasons keenly set-forth above.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments have been fully considered, but are not found persuasive.

Applicants argue that the prior art does not teach the use of colloidal, anhydrous silica (p. 7, Remarks). Applicants proffer European Pharmacopoeia which teaches that anhydrous colloidal silica is a "light, fine, white amorphous powder, with a particle size of about 15 nm." However, Applicants have provided no evidence which indicates that colloidal, anhydrous silica is not silicon dioxide as the Examiner has pointed out that silicon dioxide is colloidal and anhydrous – both compounds contain the same chemical formula. Applicants have not disputed the Examiner's assertions and have not submitted evidence or arguments which compares silicon dioxide to 'colloidal anhydrous silica' to demonstrate any difference between them.

Applicants additionally argue that "Struengmann merely mentions colloidal, anhydrous silica may be used as a tablet additive…[t]here is no teaching or suggestion…to employ a dried extract consisting essentially of leaves and about 2.5% to about 7.5% by weight of colloidal, anhydrous silica produced in a drying process comprising the steps of adding colloidal, anhydrous silica during the drying process." "At most, the combination…results in a tablet having 2% colloidal, anhydrous silica as an additive…[this] …cannot result in the subject matter of amended claim 1…about 2.5% to about 7.5%.." (p. 8, Remarks).

However, it is first noted that the claims state 'about 2.5%.' 2% is, in the opinion of the Examiner, within the realm of 'about 2.5%.' Further, even if the claim did not state 'about' 2% is very close to 2.5% and adjustment of a carrier such as colloidal anhydrous silica would have been well within the purview of the ordinary artisan at the time the Invention was made. The ordinary artisan would have been aware of the consequences of adjusting the amount of silica in a tablet slated for oral administration. The prior art makes clear that adjusting carriers such as silica in tablets is routine and well-utilized in order to optimize tablet as well as bioavailability of the active ingredient contained in the tablet *(inter alia*).

Applicants argue that Chang was taken out of context by the Examiner (p. 9) because, as stated by Applicants, Chang states that 'powder mixtures containing up to 1% colloidal silica generally resulted in a decrease in the tensile strength' and that 'the presence of lubricants and glidants…will generally produce weak bonding.' "The increased tablet crushing strength cited by the Examiner is the exception rather than the rule" (*Id*).

Chang specifically states that "[g]lidants are usually incorporated in solid formulations to improve the flow properties of granules or powders. The possible mechanisms...include reducing surface roughness, reducing friction...reducing attractive forces...separating the host particles, reducing electrostatic forces, and acting as

moisture scavengers. The bonding properties of excipients may also be affected by colloidal silicon dioxide. Nurnberg…reported an increased mechanical strength of lactose tablets on addition of 1% colloidal silica…Chowhan et al…showed that powder mixtures containing up to 1% colloidal silica generally resulted in a decrease in the tensile strength and an increase in flow rate…" Hence, Applicants' cited excerpts from Chang appear to misrepresent the entirety of the teachings of Chang. Further, it is clear from the prior art that glidants such as silicas are not used alone in tablet manufacture. Clearly, additional excipients and binders are used to adhere the table together.

Thus, although Applicants state that the binding properties associated with the use of colloidal anhydrous silica 'is the exception rather than the rule' it is clear from the prior art that the use of colloidal silica may result in increased tablet strength. Thus, it is expected that silicas will increase the tablet strength under some circumstances. As reported by Cheng et al., Nurnberg also observed an increased mechanical strength of lactose tablets using 1% colloidal silica. Cheng et al. clearly report that "…flowability and compactability of powders may be sensitive to the concentration of colloidal silica in the system…there may be an optimum concentration of colloidal silica for optimum flowability and compactability. Addition of colloidal silica above the precise concentration results in a decreased flow and a loss of cohesion in the tablet." (Intro). Thus, it is expected that at some optimum concentration, silica will produce enhanced flowability and increase in tablet strength and discovering this optimum concentration is within the skill level of the ordinary artisan.

Applicants argue that Chang does not disclose the use of colloidal silicon dioxide of greater than 2% (p. 10, Remarks). However, it is noted that Chang et al. is not used in the rejection of the claims, but rather is used merely to show that the use of silicon dioxide would be expected to increase tablet strength at particular concentrations. It is clear that at certain percentages, silicon dioxide will decrease tablet strength, however, the silicon dioxide concentration must be taken into account with the other added excipients to the tablet. Thus, the rejection which remains standing using Esperester et al. (WO 01/28363 A1) in view of Bilgrami et al. (1993) in view of Struengmann (US 6,284,269) in view of Mathowitz, E. (1999) in view of Saslawski et al. (US 6,426, 087) in view of Abramovici et al. (US 6303626) and in view of Lieberman, H., Ed. et al. (1990). In the opinion of the Examiner, the combination of these references renders the claimed invention obvious. The conclusion of obviousness is of course weighed with secondary evidence such as the Declaration presented by Applicants on 9/25/2008

Applicants argue that the difference between the concentrations of silica between formulation I and formulation II of the Declaration filed 9/25/2008 is inconsequential "..in light of the additional 15 mg of colloidal anhydrous silica added to the red vine extract of Formulation II **during the** drying step." (p. 10, Remarks). Thus, Applicants specifically contend that the effects observed in Formulation II (Dec., 9/25/2008) was achieved because of spray drying the tablets during drying with colloidal anhydrous silicone. However, again, Esperester et al. specifically *taught the addition of excipients such as*

silica during the step of drying (p. 4, line 32- p.5, line 2). Thus, considering *arguendo,* that the result achieved between Formulation I and Formulation II was based solely on silicone being added during the drying process, this step was already carried-out in the prior art and is thus obvious.

Although Applicants contend that colloidal anhydrous silicone is different from silicone dioxide, Applicants have not provided comparison information. Further, the prior art teaches that colloidal anhydrous silicone is a type of silicone used for tablet manufacture. Considering *arguendo*, that Applicants provide information which clearly shows that colloidal anhydrous silicone is not silicone dioxide, one of ordinary skill in the art having the knowledge provided by the prior art would be motivated to use colloidal anhydrous silica in the invention of Esperester et al. because (again, considering arguendo) colloidal anhydrous silica was a known type of silica which would have acted as a functional equivalent to silicone dioxide absent evidence to the contrary. Considering, *arguendo*, that colloidal anhydrous silica is different than silicon dioxide, Applicants have not shown that silicon dioxide would not provide for the properties achieved in the Declaration of 9/25/2008.

Nevertheless, it is the opinion of the Examiner, without further information/evidence, that colloidal anhydrous silica is silicon dioxide and that because Esperester et al. disclosed the addition of silicon dioxide to the red vine extract during the drying process, that Esperester et al. taught this aspect of the Invention thus

rendering this aspect obvious. In other words, Applicants are contending that there is an unexpected result with adding colloidal anhydrous silica to the red vine extract, whereby the result would have been naturally achieved by following the direction specifically given by Esperester et al. to do so.

This reasoning further applies to Applicants' subsequent argument that the addition of crospovidone to formulation II would have been expected to decrease deterioration time (pp. 10-11, Remarks). This is further indication that the results achieved in the Declaration are provided due to the addition of colloidal anhydrous silica during the drying process which was already disclosed in the prior art. Hence, it appears that Applicants have found an unexpected property resulting from a step which was already taught in the prior art hence rendering the step obvious.

There is no indication that 1) colloidal anhydrous silica is different than silicon dioxide, 2) that if a difference were present that colloidal anhydrous silica would not be a functional equivalent of silicon dioxide, 3) that the results reported by the Declaration were achieved by any particular amount/concentration of silica (i.e., solely based on amount/concentration).

Considering the claimed invention, in light of the specification, the prior art and the extrinsic evidence provided by Applicants, it remains the opinion of the Examiner

that the claimed invention is an obvious variation of Esperester et al. Compounding pharmaceutical tablets to achieve maximum parameters such as friability and strength, which contribute to overall disintegration time and therefore stability is well-known, conventional protocol in the pharmaceutical art. "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton *KSR* 127S. Ct. at 1742.

Aqueous red vine leaf extracts were known in the art for treating venous insufficiency (Esperester et al.). Esperester et al. taught the addition of conventional carriers and excipients to create capsules or tablets for oral administration. Esperester et al. taught that the extracts were dried prior to compounding into pharmaceutical dosage forms, and that carriers such as silicon dioxide could be added during drying to facilitate further processing of the extract. The use of 2% anhydrous colloidal silica was known to be used in tablet manufacture (Abramovici et al.). 2% is, in the opinion of the Examiner 'about 2.5%' as claimed. All of the claimed additives were known tablet excipients, including the tablet film as claimed within the claimed range. Adjusting additives/excipients in tablets to achieve desired flowability, hardness, friability and bioavailability (*inter alia*) was well known and achieved through routine techniques available to those of ordinary skill working in the field of Art at the time the Invention was made.

To reiterate from above, Applicants demonstrate that spray drying a red vine extract in the presence of colloidal, anhydrous silica provides for increased storage time

of the tablet under certain conditions (Declaration). However, this step of preparation was specifically suggested by Esperester et al. and is rendered obvious because spray drying with silicon dioxide (which is the equivalent of colloidal anhydrous silica absent evidence to the contrary) would have provided for the demonstrated results.

The Supreme court has acknowledged that:

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. **If a person of ordinary skill can implement a predictable varition..103 likely bars its patentability**…if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill. A court must ask whether the improvement is more than the predictable use of prior-art elements according to their established functions…
>
> …**the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results** (see *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 U.S. 2007) emphasis added.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia Leith whose telephone number is (571) 272-0968. The examiner can normally be reached on Monday - Friday 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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